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(19) AU

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(54) BENZIMIDAZOLES

(71) ICI AUSTRALIA LIMITED

(21) 35 043/78 519 236 (22) 22.4.77

(23) 12.4.78 (24) 22.4.77

(43) 18.10.79 (44) 19.11.81

(51)<sup>2</sup> C07D 417/04 C07D 405/04 C07D 235/10 C07D 235/12  
C07D 235/26 C07D 235/28 C07D 235/32 C07D 235/24  
C07D 235/30 A61K 21/415

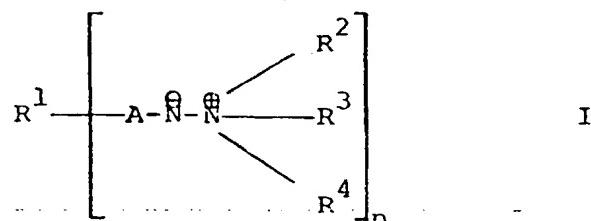
(72) Jemison, R.W., and Beames, D.J.

(74) FR

(56) 35 044/78 C07D 235/12 A61K 31/415

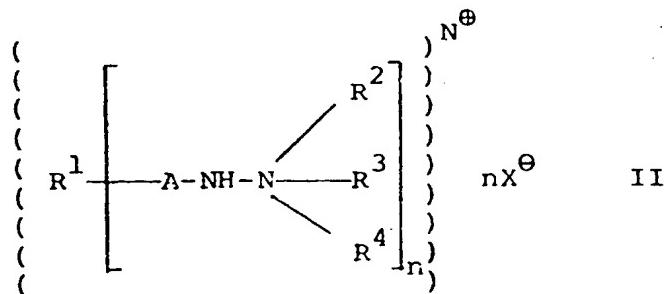
(57) The compounds have biological activity.

Claim 1. A water soluble aminimide of general formula I:



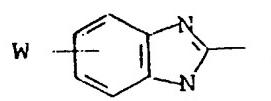
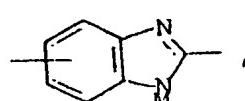
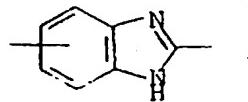
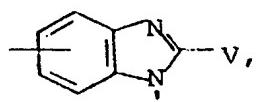
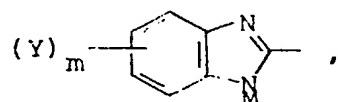
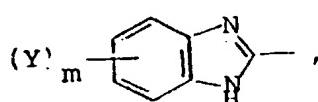
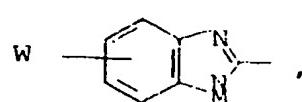
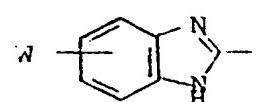
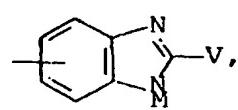
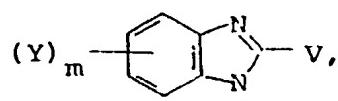
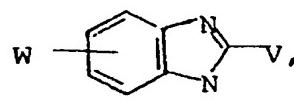
and the acid addition salt therefore of general formula II:

II:

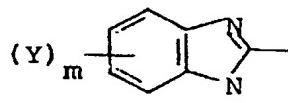


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wherein R<sup>1</sup> is a benzimidazole chosen from

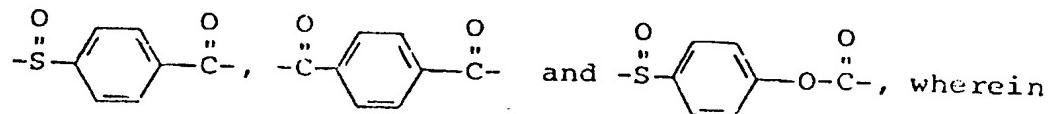
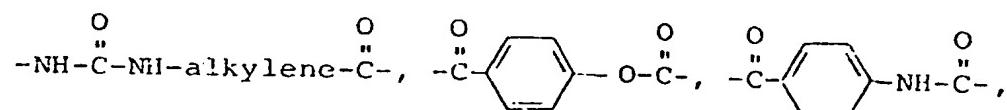
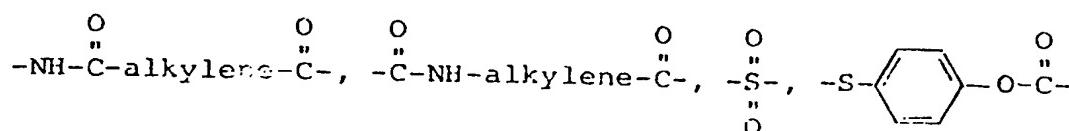
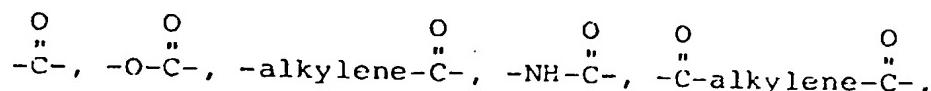


and



wherein W is hydrogen,

nitro, trifluoromethyl, C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>1</sub> to C<sub>8</sub> alkoxy, C<sub>1</sub> to C<sub>8</sub> alkylthio, amino, hydroxylamino, NHCO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, phenylthio, 4-aminophenylthio, 4-hydroxyphenylthio, phenylsulfinyl, 4-aminophenylsulfinyl, 4-hydroxyphenylsulfinyl, phenylsulfonyl, 4-aminophenylsulfonyl, 4-hydroxyphenylsulfonyl, benzoyl; Y is halogen and m is an integer from 1 to 4; V is chosen from trifluoromethyl, 4-thiazolyl, 2-furyl and NHCO<sub>2</sub>T wherein T is C<sub>1</sub> to C<sub>6</sub> alkyl; and M is the cation of an organic or inorganic base; A is chosen from



alkylene is a C<sub>1</sub> to C<sub>6</sub> alkylene group; R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently chosen from C<sub>1</sub> to C<sub>6</sub> alkyl, 2-hydroxy substituted C<sub>2</sub> to C<sub>6</sub> alkyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl, C<sub>6</sub> cycloalkyl, allyl, benzyl and phenyl; X<sup>⊖</sup> is a pharmaceutically acceptable anion; n is an integer from 1 to 3; and when n is 2 or 3 the groups -A-N-R<sup>2</sup>R<sup>3</sup>R<sup>4</sup> may be the same or different.

FORM 1

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1962



APPLICATION FOR A PATENT

COMPLETE AFTER PROVISIONAL SPECIFICATION NO. 35043/78

We, ICI AUSTRALIA LIMITED, of 1 Nicholson Street, Melbourne, Victoria, Australia, hereby apply for the grant of a Patent for an invention entitled:-

35043/78

"BENZIMIDAZOLE"

which is described in the accompanying provisional specification.

Our address for service is D.A. Freckleton, C/O ICI AUSTRALIA LIMITED, 1 Nicholson Street, Melbourne, Victoria, Australia.

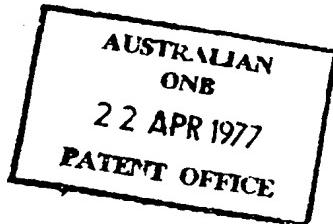
Dated this 22/4/77 day of April 1977.

ICI AUSTRALIA LIMITED,

By i.s. Patent Attorney

D.A. Freckleton.

RECEIVED  
Date 22/4/77  
Receipt No. PC 9860  
37 (10)



To: The Commissioner of Patents.

FORM 7

Regulation 12 (1)

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF AN APPLICATION

FOR A PATENT

**35043/78**

In support of the Application made by ICI AUSTRALIA

LIMITED for a patent for an invention entitled :-

"COMPOUNDS"

I, DOUGLAS ARTHUR FRECKLETON, of ICI House, 1 Nicholson Street, Melbourne, 3001, Victoria, Australia, do solemnly and sincerely declare as follows :-

1. I am authorised by ICI AUSTRALIA LIMITED, the applicant for the patent to make this declaration on its behalf.
2. ROBERT WILLIAM JEMISON, of 23 Rylandes Drive, Tullamarine, Victoria, 3043, Australia, AND DAVID JOHN BEAMES, of Flat 3, 21 Auburn Grove, Hawthorn East, Victoria, 3123, Australia,

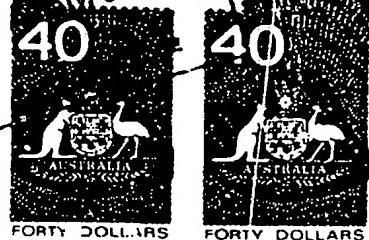
are the actual inventors of the invention and the facts upon which ICI AUSTRALIA LIMITED is entitled to make the application are as follows :-

The said ICI AUSTRALIA LIMITED is the assignee of the said actual inventors

Declared at Melbourne this // day of April 1978

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COMMONWEALTH OF AUSTRALIA  
PATENTS ACT 1952-1969



# COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Class

Int. Class

Application Number:  
Lodged:

35043/78

Complete Specification—Lodged:

Accepted:

Published:

Priority:

200  
1

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: ICI AUSTRALIA LIMITED

Address of Applicant: 1 Nicholson Street, Melbourne, Victoria, 3001, Australia.

Actual Inventors: ROBERT WILLIAM JEMISON and DAVID JOHN BEAMES

Address for Service: D A FRECKLETON, C/O ICI House, P O Box 4311, 1 Nicholson Street, Melbourne, Victoria, 3001, Australia.

Complete Specification for the invention entitled: "COMPOUNDS OF POLY(1,4-BENZODIOLIC ACID)"

The following statement is a full description of this invention, including the best method of performing it known to the inventor.

Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 9½" in depth and 6½" in width, on tough white paper of good quality and it is to be inserted inside this form.

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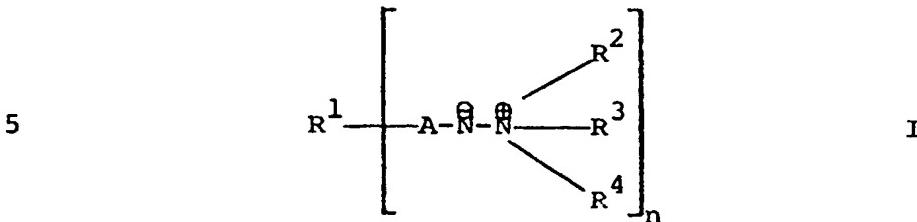
This invention relates to water soluble organic compounds having biological activity and in particular it relates water soluble benzimidazoles having anthelmintic activity.

Many organic compounds which are of use in the treatment of the diseases of men, animals and plants are essentially insoluble in water. Such compounds are often difficult to formulate and administer to the organism to be treated, and after treatment may be incompletely absorbed by or not properly dispersed within the organism.

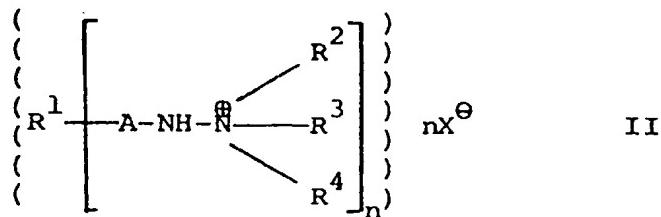
An example of the problems encountered in the administration of water insoluble compounds is found in the treatment of warm-blooded animals to control internal parasites. Many of the commercial preparations effective in the control of internal parasites, for example helminths, in warm-blooded animals comprise water insoluble organic compounds as the active ingredient(s) and as a result these preparations have to be dosed orally in the form of a tablet, bolus, capsule or drench, or in admixture with the animals food. Such oral dosage of anthelmintics can present great difficulties when large animals and/or large numbers of animals are to be treated; parenteral administration is the preferred form of dosage. Water soluble anthelmintic organic compounds are therefore of great value as such compounds may be formulated as sterile aqueous solutions suitable for administration by injection.

We have now found a class of water soluble benzimidazole compounds which show anthelmintic activity.

Accordingly we provide a water soluble aminimide of general formula I:



and the acid addition salt thereof of general formula II:



wherein R<sup>1</sup> is a group comprising a benzimidazole ring system; A is a linking group comprising at least one carbonyl or sulfonyl group directly bonded to the group -N-NR<sup>2</sup>R<sup>3</sup>R<sup>4</sup>; R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently chosen from C<sub>1</sub> to C<sub>6</sub> alkyl, 2-hydroxy substituted C<sub>2</sub> to C<sub>6</sub> alkyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl, allyl, benzyl and phenyl; X<sup>θ</sup> is a pharmaceutically acceptable organic or inorganic anion; n is an integer from 1 to 3; and when n is 2 or 3 the groups -A-N-NR<sup>2</sup>R<sup>3</sup>R<sup>4</sup> may be the same or different.

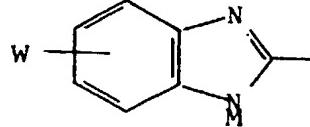
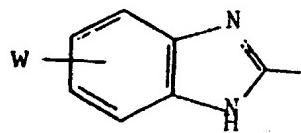
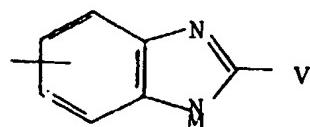
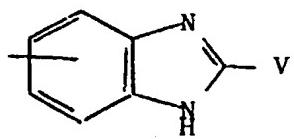
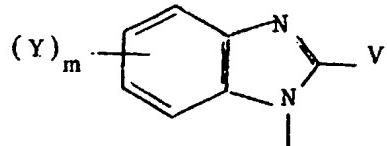
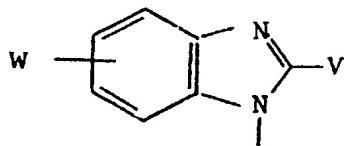
The anion X<sup>θ</sup> may be any convenient pharmaceutically acceptable anion, for example, chloride, bromide, sulfate, phosphate, nitrate, maleate, acetate, benzoate, succinate,

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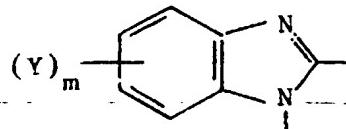
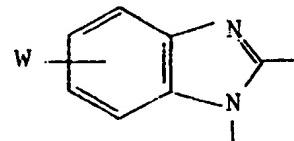
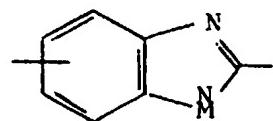
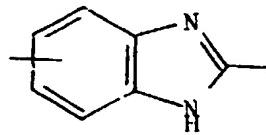
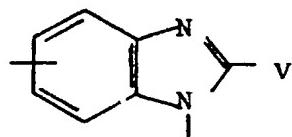
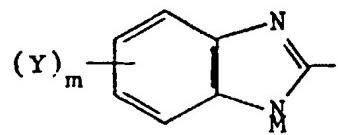
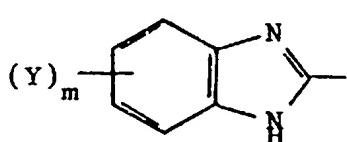
- 4 -

citrate, lactate, ascorbate and the like. The anion may be the anion of a buffering agent with which a compound of general formula I is associated in a composition. Certain of the compounds of formula I, and in particular those compounds in which the 1-position of the benzimidazole ring is unsubstituted, are acids and therefore may be in the form of a salt of a pharmaceutically acceptable inorganic or organic base. Suitable bases include for example, pharmaceutically acceptable alkali metal and alkaline earth metal hydroxides.

Typical R<sup>1</sup>- are the groups listed below which may be linked to A through the bond(s) indicated or through a suitable substituent group W:

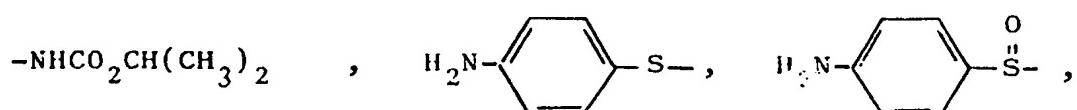


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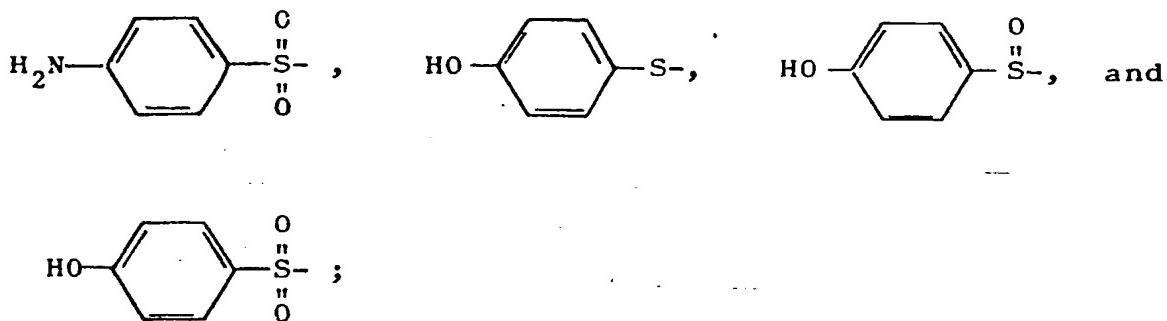
wherein W is hydrogen, nitro, trifluoromethyl, alkyl, alkoxy, alkylthio, benzoyl, phenylthio, phenylsulfinyl, phenylsulfonyl, amino, hydroxylamino,

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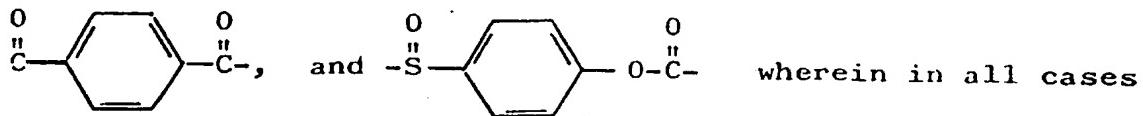
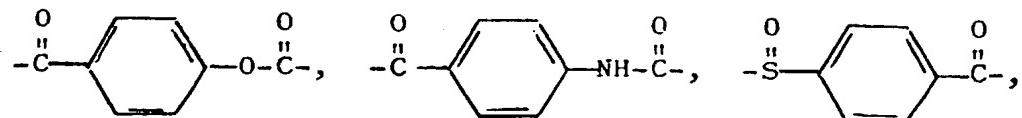
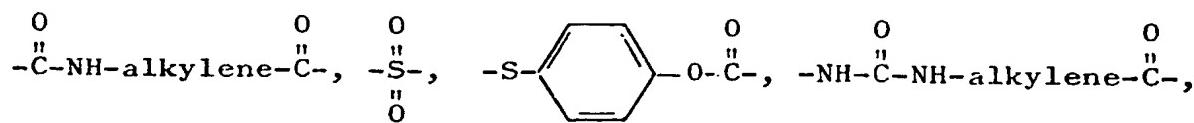
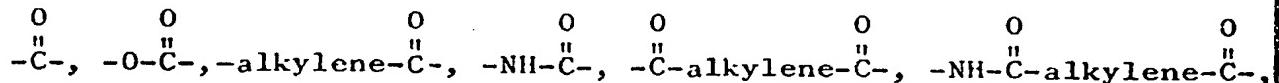
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Y is halogen and m is an integer from 1 to 4; V is chosen from  $\text{CF}_3$ , 4-thiazolyl, 2-furyl and  $\text{NHCO}_2\text{T}$  wherein T is  $\text{C}_1$  to  $\text{C}_6$  alkyl; and M is the cation of an organic or inorganic base.

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Typical linking groups A are, for example:



the group  $-\overset{\text{O}}{\underset{\text{||}}{\text{N}}}\text{-NR}^2\text{R}^3\text{R}^4$  is attached to A through a carbonyl or

sulfonyl group of A.

Preferred A are:

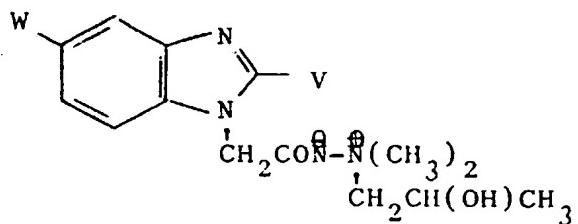
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$\begin{matrix} \text{O} & \text{O} \\ \parallel & \parallel \\ -\text{NH}-\text{C}-, & -\text{C}-, & -\text{alkylene}-\text{C}-, & -\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{NH}-\text{alkylene}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}- \end{matrix}$  and  
 $\begin{matrix} \text{O} & \text{O} \\ \parallel & \parallel \\ -\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{alkylene}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-, \end{matrix}$  wherein the term -alkylene- means a C<sub>1</sub> to C<sub>6</sub> alkylene group.

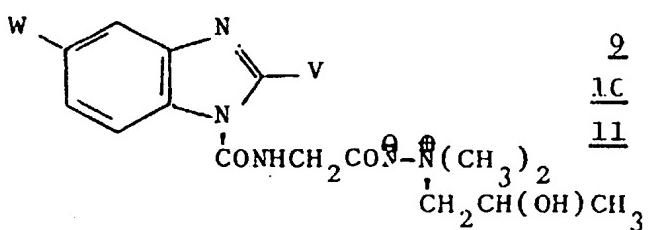
Typical R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are C<sub>1</sub> to C<sub>6</sub> alkyl, C<sub>6</sub> cycloalkyl, 2-hydroxyalkyl, 2,3-dihydroxyalkyl, 3-chloro-2-hydroxypropyl, allyl, benzyl and phenyl.

Preferred R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are methyl, 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl and allyl.

Specific compounds embraced by our invention include:

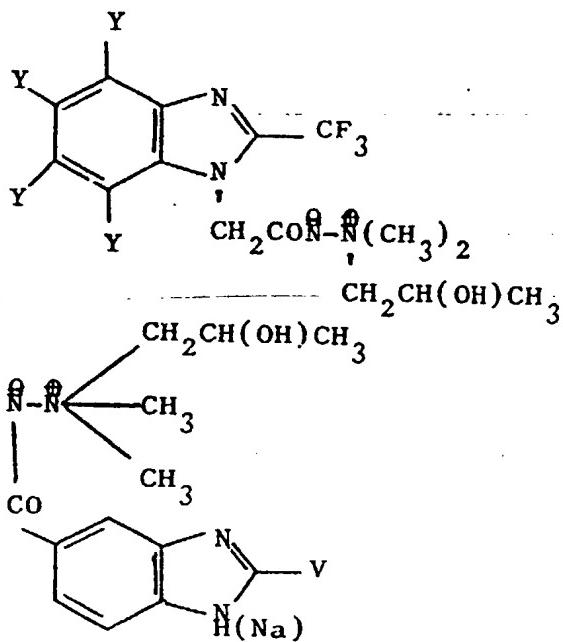


- 1 W=H, V=CF<sub>3</sub>  
2 W=H, V=4-thiazolyl  
3 W=H, V=NHCO<sub>2</sub>CH<sub>3</sub>  
4 W=NO<sub>2</sub>, V=CF<sub>3</sub>  
5 W=C<sub>3</sub>H<sub>7</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>  
6 W=C<sub>6</sub>H<sub>5</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>  
7 W=C<sub>6</sub>H<sub>5</sub>S(O), V=NHCO<sub>2</sub>CH<sub>3</sub>  
8 W=4-(Na)HO-C<sub>6</sub>H<sub>4</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>



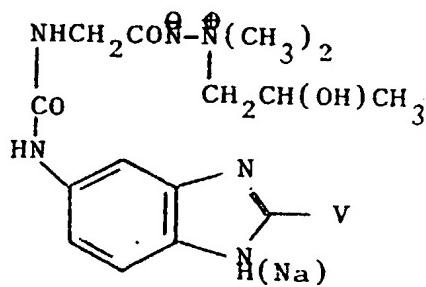
- 9 W=H, V=NHCO<sub>2</sub>CH<sub>3</sub>  
10 W=C<sub>3</sub>H<sub>7</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>  
11 W=C<sub>6</sub>H<sub>5</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>  
12 W=C<sub>6</sub>H<sub>5</sub>S(O), V=NHCO<sub>2</sub>CH<sub>3</sub>  
13 W=4-(Na)HO-C<sub>6</sub>H<sub>4</sub>S, V=NHCO<sub>2</sub>CH<sub>3</sub>

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14  $\text{Y}=\text{Cl}$

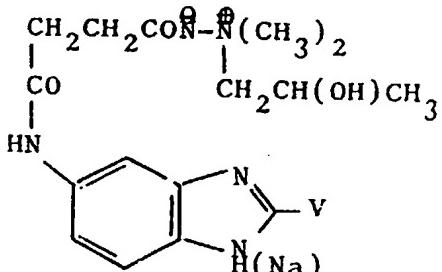
15  $\text{Y}=\text{Br}$



16  $\text{V}=\text{NHCO}_2\text{CH}_3$

17  $\text{V}=\text{CF}_3$

18  $\text{V}=4\text{-thiazolyl}$



19  $\text{V}=\text{CF}_3$

20  $\text{V}=4\text{-thiazolyl}$

21  $\text{V}=\text{NHCO}_2\text{CH}_3$

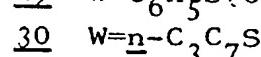
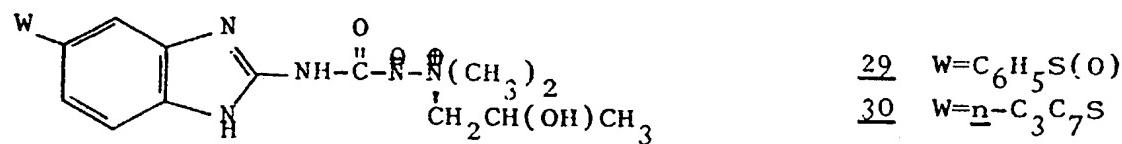
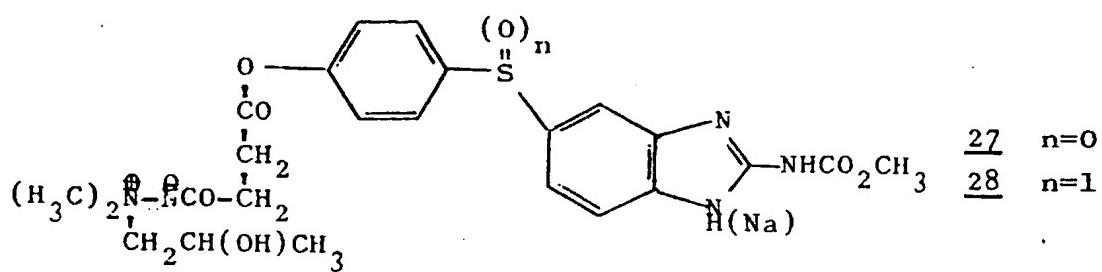
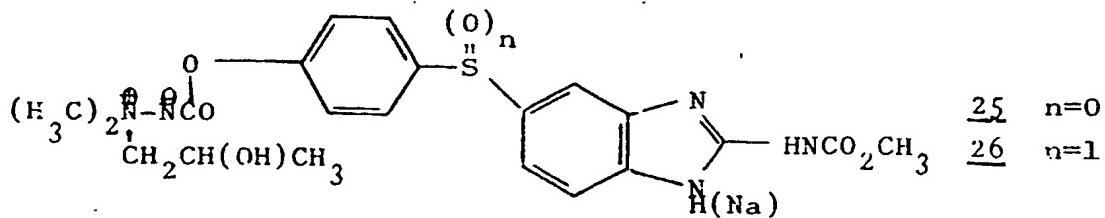
22  $\text{V}=\text{CF}_3$

23  $\text{V}=4\text{-thiazolyl}$

24  $\text{V}=\text{NHCO}_2\text{CH}_3$

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The compounds of the invention may be prepared by forming the aminimide derivative of an organic acid ester, acid halide or acid hydrazide (e.g. the esters, halides and hydrazides of carboxylic and sulfonic acids). Thus the compounds of the invention may be prepared directly from a water insoluble organic compound containing a benzimidazole ring system and bearing an acid ester, acid halide or acid hydrazide group according to the following reaction scheme:



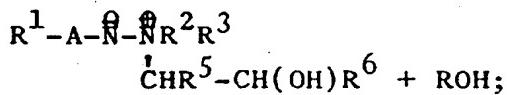
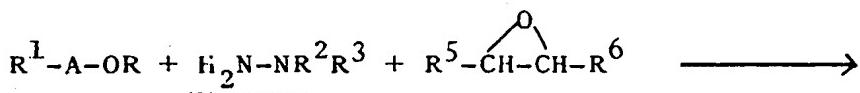
wherein R<sup>1</sup> and A as hereinbefore defined and B is a group which may be converted to or replaced by the group -N-N<sup>2</sup>R<sup>3</sup>R<sup>4</sup> as hereinbefore defined.

Suitable B include halo, alkoxy, aryloxy, aralkoxy, and  $-\text{NH}-\text{NR}^2\text{R}^3$  wherein  $\text{R}^2$  and  $\text{R}^3$  are as hereinbefore defined.

Accordingly we provide a process for the preparation of the compounds of the invention which process comprises reacting a water insoluble organic compound comprising a benzimidazole ring system and bearing at least one acid ester, acid halide or acid hydrazide group to form the aminimide derivative of said acid ester, acid halide or acid hydrazide group.

Examples of the process include:

- a) reaction of an acid ester with hydrazine, a mono-substituted hydrazine or an unsymmetrically disubstituted hydrazine and an alkylene oxide to form said water soluble aminimide in accordance with the following reaction scheme

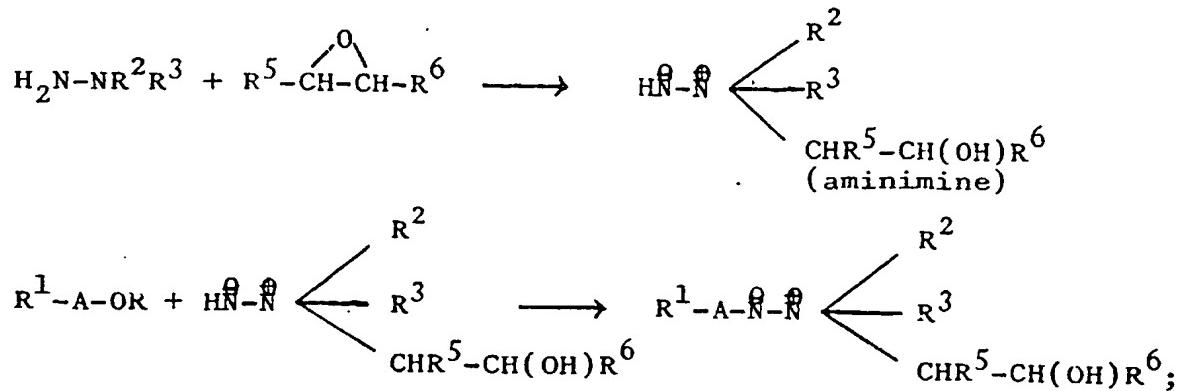


- b) reaction of hydrazine, a mono- substituted hydrazine or an unsymmetrically disubstituted hydrazine with an alkylene oxide to form an aminimine and reaction of said aminimine with an acid ester to form said water soluble aminimide in

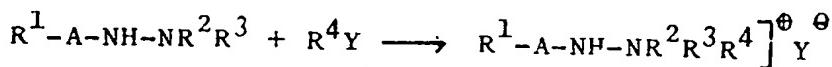
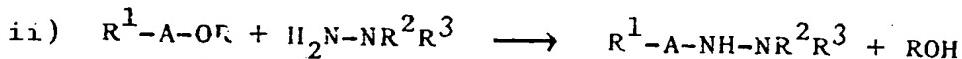
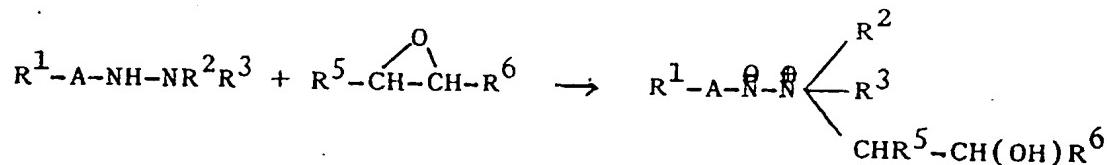
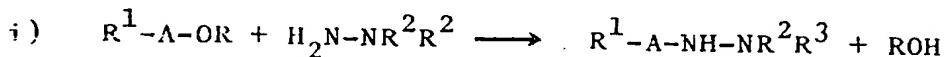
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accordance with the following reaction scheme



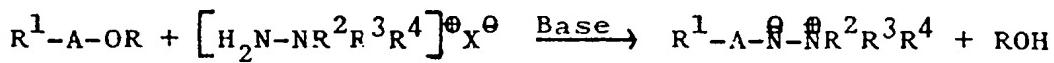
c) reaction of an acid halide or an acid ester with hydrazine, a mono- substituted hydrazine or an unsymmetrically di- substituted hydrazine to form an acid hydrazide derivative and reaction of said acid hydrazide group with an alkylating agent (suitable alkylating agents include, for example, alkylene oxides, the alkyl, allyl and benzyl halides, alkyl sulfates and etc) to form said water soluble aminimide in accordance with the following reaction schemes.



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- d) reaction of an acid ester or an acid halide with a 1,1,1-trisubstituted hydrazinium salt in the presence of a base to form said water soluble aminimide derivative in accordance with the following reaction scheme



It should be noted that where the water insoluble organic compound comprising a benzimidazole ~~ring system~~ bears more than one acid ester, acid halide or acid hydrazide group, for example the precursors to the compounds of the invention numbers 10, 11, 12 and 13, the product of the preparation of the water soluble aminimide derivative may comprise: a single aminimide derivative from preferential reaction of one acid ester, acid halide or acid hydrazide group; a mixture of different aminimide derivatives each bearing one aminimide group; a single aminimide derivative bearing more than one aminimide group; or mixtures thereof.

Where the water insoluble organic compound containing a benzimidazole ~~ring system~~ does not bear an acid halide, acid ester or acid hydrazide group, a water soluble aminimide derivative of that compound may still be prepared provided an acid ester, acid halide or acid hydrazide derivative of that compound can be prepared. For example, water soluble compounds

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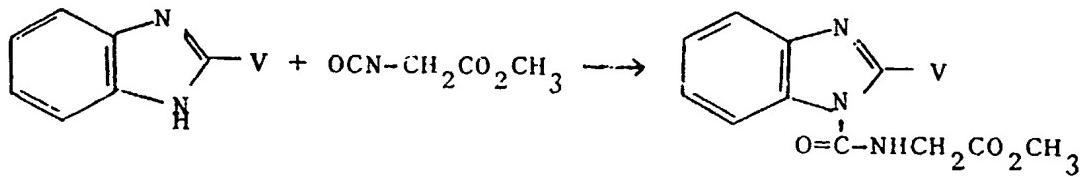
of the invention may be prepared from water insoluble benzimidazole compounds  $R^1H$  which do not bear an acid ester, acid halide or acid hydrazide group but bear an acidic hydrogen, by:

- 5      a) reacting a water insoluble organic compound  $R^1-H$  bearing an acidic hydrogen with a reagent bearing an acid ester, acid halide or acid hydrazide group to replace the acidic hydrogen with a linking group bearing an acid ester, acid halide or acid hydrazide group: and
- 10     b) treating the acid ester, acid halide or acid hydrazide derivative of  $R^1-H$  obtained in a) to form the aminimide derivative  $R^1-A-\overset{\oplus}{N}-\ddot{N}R^2R^3R^4$  wherein  $R^1$ , A,  $R^2$ ,  $R^3$  and  $R^4$  are as hereinbefore defined.

The term "acidic hydrogen" is used to mean that  $R^1H$  is an organic acid with a pKa of less than 35. Thus the definition embraces the normal organic acids such as phenols, the weak organic acids such as alcohols, and the very weak organic "carbon" acids.

For example:

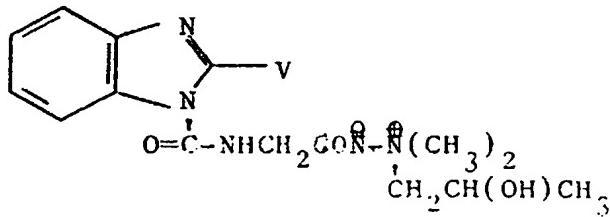
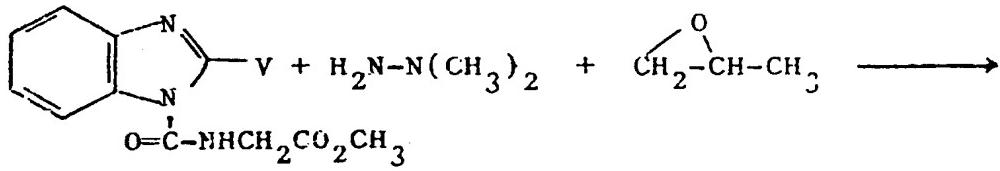
Step (a)



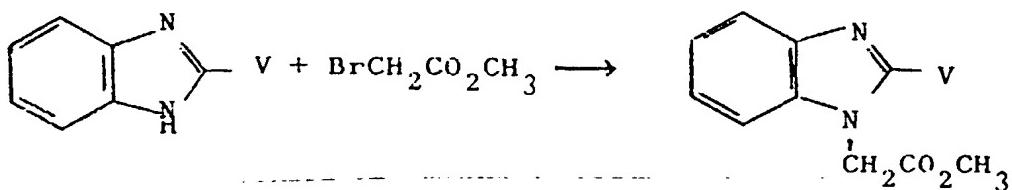
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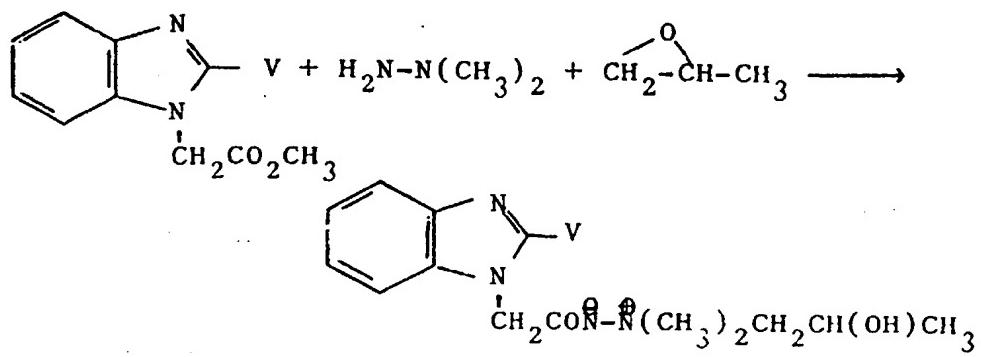
Step (b)



Step (a)



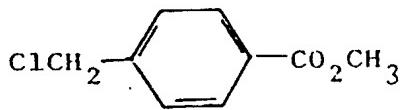
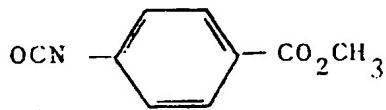
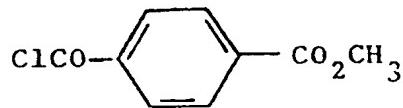
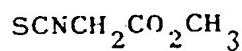
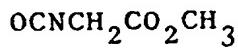
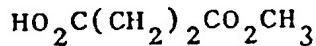
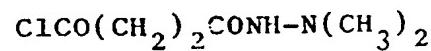
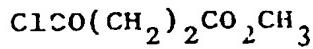
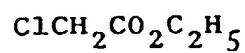
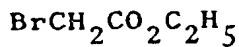
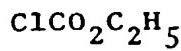
Step (b)



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Reagents suitable for reaction with a water insoluble compound bearing an acidic hydrogen to form a linking group bearing an acid halide, acid ester or acid hydrazide group (step (a) above) include, for example:



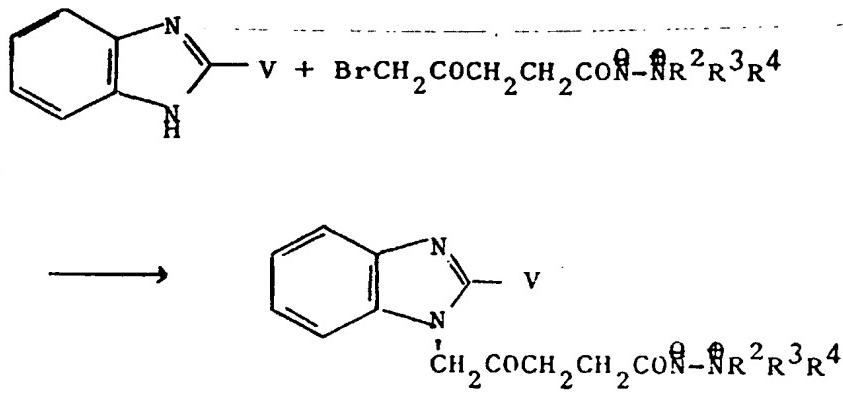
In an alternative process a water soluble compound of the invention may be prepared directly from a water insoluble benzimidazole compound  $\text{R}^1\text{H}$ , which does not bear an acid ester, acid halide or acid hydrazide group but which bears an acidic hydrogen, by reaction of  $\text{R}^1\text{H}$  with a reagent  $\text{QAN}-\overset{\theta}{\text{NR}}^2\text{R}^3\text{R}^4$

wherein A, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as hereinbefore defined and Q is a group or atom which undergoes reaction with or displacement by said acidic hydrogen compound thereby replacing said acidic hydrogen with the group -A-N-Q-R<sup>2</sup>R<sup>3</sup>R<sup>4</sup>.

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For example:

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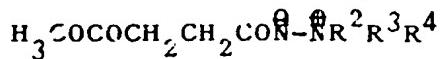
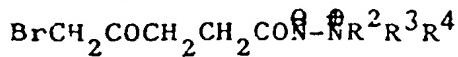


Thus water insoluble organic compounds R<sup>1</sup>-H bearing an acidic hydrogen in the form of, for example, an alcohol, phenol or amine group may be converted to a compound of the invention by reaction with a reagent bearing, for example, acid ester,  $\alpha$ -haloketo-, alkyl halide, acyl halide or isocyanate group and an aminimide group.

5.

Suitable Q include, for example, groups such as isocyanate, isothiocyanate, alkoxy, aryloxy, arylalkoxy and atoms such as halogen.

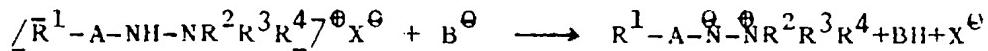
Reagents of the formula QA-N-Q-R<sup>2</sup>R<sup>3</sup>R<sup>4</sup> suitable for reaction with a water insoluble organic compound bearing an acidic hydrogen include, for example



It will be evident to those skilled in the art that the compounds of the invention are able to exist in zwitterionic (ylide) form or in a cationic form. The zwitterionic form may be converted to the cationic form by treatment with an inorganic or organic acid according to the following reaction scheme.



This reaction is reversible and thus the cationic form may be converted to the zwitterionic form by treatment with a suitable base according to the following reaction scheme



We have found that the compounds of the invention are active against a wide range of internal parasites which infect warm-blooded animals. These compounds are particularly effective in the treatment of nematodes such as Haemonchus contortus, Ostertagia spp, Trichostrongylus spp, Cooperia spp, Nematodirus spp, Chabertia ovina, Tunostomum spp, Strongyloides, Oesophagostomum spp and Dictyocaulus spp.

Accordingly in a further aspect of our invention we provide a method of treating warm-blooded animals to

eradicate certain internal parasites which method comprises administering to said warm-blooded animals a therapeutic dose of a composition comprising as active ingredient a compound of general formula I or II, as hereinbefore defined.

For effective treatment, certain dosage levels are desired depending upon the compound employed, the type of animal to be treated, and the particular helminth being combatted. In general, efficacy is achieved when the composition is administered in a single dose at dosage levels of from about 1 to 100 mg active ingredient per kg of animal body weight.

The compounds of the invention may be used on their own to treat warm-blooded animals to eradicate internal parasites but are preferably administered in the form of a composition.

Thus in yet a further aspect the invention provides a composition for the treatment of warm-blooded animals to eradicate certain internal parasites said composition comprising as active ingredient a compound of general formula I or II, as hereinbefore defined, and a carrier therefor.

The compositions of the present invention may be administered in a variety of ways, depending upon the particular animal employed, the type of anthelmintic treatment normally given to such an animal, the materials employed, and the particular helminths being combatted. It is preferred

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to administer them in a single efficacious dose at a time when helminth infection is apparent or suspected. They may be employed alone or in combination with other anthelmintics, parasiticides or antibacterials. The amounts of the active 5 anthelmintic ingredient in the composition, as well as the remaining constituents are varied according to the type of treatment to be employed, the host animal, and the particular parasitic disease being treated. In general, however, compositions containing a total weight percent of the active compound or compounds ranging from 0.001 to 95% will be suitable with the remainder being any suitable carrier or vehicle. Furthermore, the compositions should contain enough of the active ingredients to provide an effective dosage for the proper treatment of the parasitic disease.

15 Preferably the compositions are administered to the animal by parenteral dose and in a further aspect of our invention we provide an injectable composition comprising a sterile aqueous solution of a compound of general formula I or II.

20 The injectable composition may comprise other water soluble veterinary drugs, stabilizers, buffering agents and the like and may be sterilized by methods known to those skilled in the art for the sterilization of injectable solutions such as, for example, ultra filtration or gamma radiation. For convenience, the active ingredient usually

comprises 5 to 80% by weight of the total sterile aqueous solution.

A number of other modes of treatment may be employed, and each to some extent determines the general nature of the composition. For example, the anthelmintic compositions may be administered to domesticated animals in single unit oral dosage form such as a tablet, bolus, capsule or drench; in a "pour-on" form suitable for dermal application; or they may be compounded as feed premix to be later admixed with the animal's food.

When the compositions are to be solid unit dosage forms as in tablets, capsules, or boluses, the ingredients other than the active ingredient may be any other pharmaceutically acceptable vehicles convenient in the preparation of such forms, and preferably materials nutritionally suitable such as starch, lactose, talc, magnesium stearate, vegetable gums, and the like. Moreover when capsules are employed, the active compound may be used in essentially undiluted form, the only extraneous material being that of the capsule casing itself which may be hard or soft gelatin or any other pharmaceutically acceptable encapsulating material. In all of such forms, i.e. in tablets, boluses and capsules, the active compound conveniently ranges from about 5 to 80% by weight of the total composition.

When the unit dosage form is to be in the form of a

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drench, the active ingredient may be mixed with agents which will aid in the subsequent suspending of the active compound in water, such as bentonite, clays, water-soluble starch, cellulose derivatives, gums, surface active agents and the like to form a dry predrench composition, and this predrench composition added to water just before use. In the predrench formulation, in addition to the suspending agent, such ingredients as preservatives, antifoam compounds, and the like may be employed. Such a dry product may contain as much as 95% by weight of the active compound, the rest being contributed by the excipients. Preferably, the solid composition contains from 30% to 95% by weight of the active compound. Enough water should be added to the solid product to provide the proper dosage level within a convenient amount of liquid for a single oral dose. Liquid drench formulations containing from about 10 to 50 weight percent of dry ingredients will in general be suitable with the preferred range being from 15 to 30 weight percent. Where the compositions are intended to be used as feeds, feed supplements, or feed premixes, they will be mixed with suitable ingredients of an animal's nutrient ration. The solid orally-ingestible carriers normally used for such purposes, such as distillers' dried grains, corn meal, citrus meal, fermentation residues, ground oyster shells, Attapulgus clay, wheat shorts, molasses solubles, corn cob meal, edible vegetable substances, toasted

dehulled soya flour, soybean mill feed, antibiotics mycelia, soya grits, crushed limestone and the like are all suitable. The active compounds are intimately dispersed or admixed throughout the solid inert carrier by methods such as grinding, stirring, milling or tumbling. By selecting proper diluents and by altering the ratio of carrier to active ingredient, compositions of any desired concentration may be prepared.

5 Feed supplement formulations containing from about 10 to 30% by weight of active ingredient are particularly suitable for

10 addition to feeds. The active compound is normally dispersed or mixed uniformly in the diluent but in some instances may be adsorbed on the carrier.

These supplements are added to the finished animal feed in an amount adequate to give the final concentration of active ingredient desired for controlling or treating the helminth infection by way of the animal ration. Although the preferred level in feeds will depend on the particular compounds being employed, the active ingredients of this invention are normally fed at levels of 0.05 - 25% in the feed. As stated above, animals are preferably treated at a time when the infestation is apparent or suspected and the most preferred method for such treatment is via the single oral dose technique. Thus administration of medicated feed is not preferred but may certainly be employed. Similarly, the amounts of drug present in the feed may be reduced to levels in the order of

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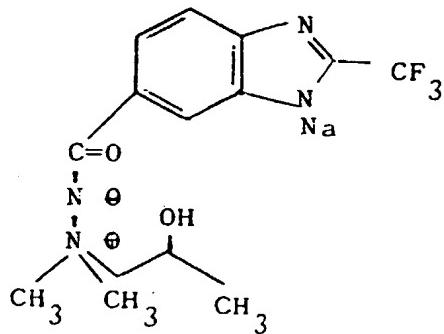
0.001% to 3.0 weight percent based on the weight of feed, and the medicated feed administered over prolonged periods. This would be in the nature of a preventive or prophylactic measure but again is not the mode of choice. Another method of administering the compositions of this invention to animals whose feeds are conveniently pelleted, such as sheep, is to incorporate them directly in the pellets. For instance, the compositions are readily incorporated in nutritionally adequate alfalfa pellets at levels of 2 to 110 grams per pound of pellets for therapeutic use, and at lower levels for example 80 to 1000 milligrams per pound for prophylactic use, and such pellets fed to the animals.

..  
The compositions may also optionally contain other  
drugs of veterinary utility. Examples of these veterinary drugs  
15 which may be present in the veterinary compositions of this  
invention, depending upon the mode of administration of the said  
compositions, include piperazine, 1-diethyl-carbamyl-4-methyl-  
piperazine, tetrachloroethylene, organic and inorganic arsenical  
compounds, tetramisole, 2-phenyl-benzimidazole, thiabendazole,  
50 phenothiazine, mebendazole, pyrantel salts and nitrophenols.  
..

The invention is now illustrated by, but by no means limited to, the following examples in which all parts are parts by weight unless otherwise specified. The proton magnetic resonance (pmr) spectra were determined in deuterio-chloroform, d<sub>6</sub>-dimethylsulfoxide or mixtures thereof with D<sub>2</sub>O exchange where appropriate unless otherwise specified.

Example 1

Preparation of



10 1,1-Dimethyl-1-(2-hydroxypropyl)amine-2'-trifluoromethyl-5'-benzimidazole carboximide. Sodium Salt. (17)

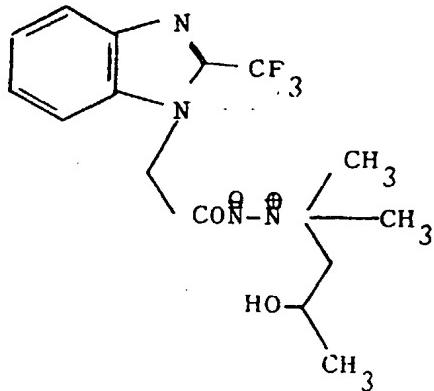
A mixture of methyl 2-trifluoromethyl 5-benzimidazole carboxylate (150 parts), dimethyl hydrazine (45 parts), propylene oxide (45 parts), sodium methoxide (41 parts) and t-butyl alcohol (750 parts) was stirred at 55°C for 24 hours. The mixture was diluted with methanol (500 parts), filtered, and the solvent removed "in vacuo" to afford the title compound (as the sodium salt) as a glassy hygroscopic, water

soluble solid. Infra red spectrum showed bands at  $1590\text{ cm}^{-1}$  (aminimide) and  $3300\text{ cm}^{-1}$  (OH).

Example 2

Preparation of

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1,1-Dimethyl-1-(2-hydroxypropyl)amine-2'-trifluoromethylbenzimidazolyl-1'-acetimide. (1)

(a) A solution of 2-trifluoromethylbenzimidazole (20 parts) in acetonitrile (220 parts) was treated with solid sodium methoxide (7 parts) and then allowed to stir at room temperature for 0.5 hr. The mixture was treated with ethyl bromoacetate (22 parts) and allowed to stir at  $50^{\circ}\text{C}$  overnight. Chloroform (150 parts) was added to the cooled (room temperature) solution and the mixture filtered and concentrated in vacuo. The residue was dissolved in chloroform, filtered again and the solvent removed to give ethyl 2-trifluoromethylbenzimidazolyl-1-acetate as a crystalline solid (24 parts) m.p.  $48^{\circ}\text{C}$ .

Infra red spectrum (nujol): 1740 cm<sup>-1</sup> (carbonyl). Pmr spectrum (δ ppm): 1.35 (t, 3H), 4.7 (q, 2H), 5.5 (s, 2H), 8.1 (m, 3H), 8.7 (m, 1H).

- (b) A mixture of ethyl 2-trifluoromethyl-1-benzimidazolyl acetate (100 parts), dimethyl hydrazine (29 parts), propylene oxide (29 parts) and t-butyl alcohol (500 parts) was stirred at 60°C for 24 hours. The reaction mixture was diluted with methanol, filtered, and the solvent removed "in vacuo" to give the title compound (139 parts) as a viscous water soluble oil. Infra red spectrum 1620 cm<sup>-1</sup> (aminimide) and 3300 cm<sup>-1</sup> (OH). Partial pmr spectrum (δ ppm): 1.2 (d, 3H), 3.8 (s, 6H), 5.25 (s, 2H).

Example 3

- (a) Ethyl 2-trifluoromethyl-5-nitrobenzimidazolyl-1-acetate, ethyl 5,6,7,8-tetrabromo-2-trifluoromethylbenzimidazolyl-1-acetate and ethyl 5,6,7,8-tetrachloro-2-trifluoromethylbenzimidazolyl-1-acetate were prepared from the respective benzimidazoles following an analogous procedure to that described in Example 2 for the preparation of ethyl 2-trifluoromethylbenzimidazolyl-1-acetate from 2-trifluoromethylbenzimidazole.

Ethyl 2-trifluoromethyl-5-nitrobenzimidazolyl-1-acetate:

Pale yellow solid

Infra red spectrum (nujol) 1740, 1600, 1020, 1000 cm<sup>-1</sup>

Partial pmr spectrum (δ ppm) 1.3 (t, 3H), 4.35 (2 x q, 2H) 5.25 (s, 2H), 7.5-9.0 (3H)

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Ethyl 5,6,7,8-tetrabromo-2-trifluoromethylbenzimidazolyl-1-acetate:

m.p. 197°C white crystalline solid

Infra red spectrum (nujol) 1740, 1000 and 985 cm<sup>-1</sup>

Partial pmr spectrum ( $\delta$  ppm) 3.85 (s, 3H), 5.45 (s, 2H)

Ethyl 5,6,7,8-tetrachloro-2-trifluoromethylbenzimidazolyl-1-acetate:

m.p. 153°C white crystalline solid

Infra red spectrum (nujol) 1745, 1050, 950, 840 and 815 cm<sup>-1</sup>

Partial pmr spectrum ( $\delta$  ppm) 3.8 (s, 3H), 5.4 (s, 2H)

- (b) The 1,1-dimethyl-1-(2-hydroxypropyl)aminimide derivatives of ethyl 2-trifluoromethyl-5-nitrobenzimidazolyl-1-acetate, ethyl 5,6,7,8-tetrabromo-2-trifluoromethylbenzimidazolyl-1-acetate and ethyl 5,6,7,8-tetrachloro-2-trifluoromethylbenzimidazolyl-1-acetate (i.e. the aminimides of structure 4, 15 and 14 respectively) were prepared following an analogous procedure to that described in Example 2 for the preparation of the 1,1-dimethyl-1-(2-hydroxypropyl)aminimide derivative (1) of ethyl 2-trifluoromethylbenzimidazolyl-1-acetate.

1,1-Dimethyl-1-(2-hydroxypropyl)amine-2'-trifluoromethyl-5'-nitrobenzimidazolyl-1'-acetimide (4)

Viscous water soluble oil

Infra red spectrum (film) 3350, 1620 cm<sup>-1</sup>

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1,1-Dimethyl-1-(2-hydroxypropyl)amine-5',6',7',8'-tetrabromo-2'-trifluoromethylbenzimidazolyl-1'-acetimide (15)

Water soluble, crystalline solid after chromatography on alumina; mp 218°C. Infra red spectrum (nujol) 3200, 5 1610, 1000, 820 and 790  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 1.05 (d, 3H), 3.40 (d, 6H) 4.3 (m, 1H) and 5.15 (s, 2H).

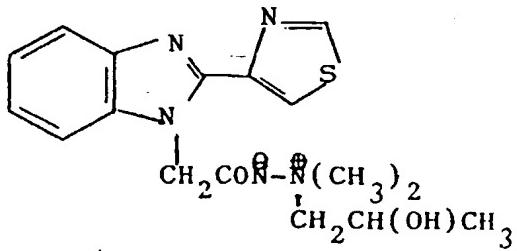
1,1-Dimethyl-1-(2-hydroxypropyl)amine-5',6',7',8'-tetrachloro-2'-trifluoromethylbenzimidazolyl-1'-acetimide (14)

Water soluble, crystalline solid after chromatography on alumina; mp 181°C. Infrared spectrum (nujol) 3250, 1625, 1000, 840 and 810  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 1.15 (d, 3H), 3.2 (m, 2H) 3.45 (d, 6H), 4.3 (m, 1H) and 5.15 (s, 2H).

15 Example 4

Preparation of



1,1-Dimethyl-1-(2-hydroxypropyl)amine-2'-(4"-thiazolyl)-benzimidazolyl-1'-acetimide (2)

(a) A slurry of "Thiabendazole" [2-(4"-thiazolyl)

20 benzimidazole] (108 parts) in acetonitrile (1000 parts)

was treated at room temperature with sodium methoxide (32 parts). After 30 min the stirred mixture was treated with ethyl chloroacetate (72 parts) and the temperature of the mixture raised to 70°C. The mixture was stirred and heated at 70°C for 48 hr, then cooled, the solvent removed and the product extracted with chloroform. Crystallization afforded the product as an approximately 1:1 mixture of methyl and ethyl esters which was used without further purification for the preparation of the aminimides.

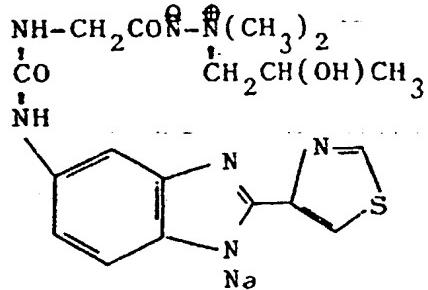
Infra red spectrum (nujol) 1740 cm<sup>-1</sup> (carbonyl).

Partial pmr spectrum ( $\delta$  ppm) 5.7 (s, 2H), 8.5 (d, 1H)  
9.0 (d, 1H).

- (b) A mixture of methyl (and ethyl) 2-(4'-thiazolyl) benzimidazolyl-1-acetate (50 parts) dimethylhydrazine (14 parts) propylene oxide (14 parts) and t-butyl alcohol (250 parts) was stirred at 50°C for 6 hours. The reaction mixture was diluted with methanol, filtered and the solvent removed in vacuo to afford the title compound (69 parts) as a glassy water-soluble solid. Infra red spectrum (film) 3300 cm<sup>-1</sup> (OH broad) and 1600 cm<sup>-1</sup> (aminimide carbonyl). Partial pmr spectrum ( $\delta$  ppm) 1.1 (d, 3H), 3.4 (s, 6H), 5.4 (s, 2H).

### Example 5

### **Preparation of**



Sodium salt of the aminimide derived from 1-methoxycarbonyl-methyl-3-[5'-[2'-(4"-thiazolyl) benzimidazolyl]] urea (20)

- (a) A slurry of 5-amino-2-(4'-thiazolyl) benzimidazole (43 parts) in dry tetrahydrofuran (500 parts) was warmed to 50°C and then the stirred mixture was treated dropwise with methyl isocyanatoacetate (25 parts). The mixture was heated at 50°C overnight then cooled, and poured into water. The solid product was collected, washed well with water, and dried in a vacuum oven.

1-Methoxycarbonylmethyl-3-[5'-2'-(4"-thiazolyl) benzimidazole] urea (52 parts) as a cream coloured powder.

Infra red spectrum (nujol) 3320, 3280, 1725 and 1630  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 3.7 (s, 3H), 3.9 (s, 2H).

- (b) A mixture of dimethylhydrazine (8.0 parts), propylene oxide (8.8 parts), sodium methoxide (4.0 parts) and t-butyl alcohol (60 parts) was treated with 1-methoxy-

carbonylmethyl-3-[5'-[2'-(4"-thiazolyl) benzimidazole]  
urea (22.5 parts) and the mixture stirred at 60°C for  
72 hours. The solvent was removed in vacuo, methanol  
was added and the solution was filtered. Benzene was  
added to the filtrate and the mixture evaporated to  
dryness. The solid product was collected and washed  
several times with ether to afford the title compound (35.6  
parts) a hygroscopic, water-soluble, amber coloured solid.  
Infra red spectrum (film) 3300 cm<sup>-1</sup>, 1650-1600 cm<sup>-1</sup> (broad).

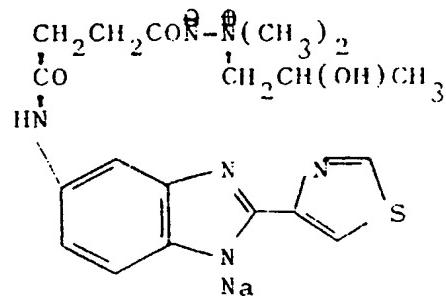
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Example 6

Preparation of



Sodium salt of the aminimide derived from 2-(4'-thiazolyl)-5-[ $\beta$ -(methoxycarbonyl)propionylamino] benzimidazole (23).

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- (a) A stirred solution of 5-amino-2-(4'-thiazolyl) benzimidazole (60 parts) in dry pyridine (300 parts) was cooled to -10°C and treated dropwise during five minutes with monomethyl succinoyl chloride (60 parts). The temperature of the mixture was allowed to rise to room temperature while stirring during 1.5 hr. The mixture was cooled to a temperature of 0°C and treated dropwise with water

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(20 parts). The temperature of the mixture was allowed to warm to room temperature (0.5 hr) and then poured onto ice and the aqueous solution extracted with ethyl acetate ( $\leq$  20,000 parts). (It was necessary to add a considerable quantity of sodium chloride to the mixture to assist the extraction).

The dried extract was concentrated in vacuo and the residue dissolved in methanol/toluene and the solvent removed by distillation. The azeotropic distillation was repeated twice to remove the last traces of pyridine.

2-(4'-Thiazolyl)-5-[ $\beta$ -(methoxycarbonyl)propionylamino]-benzimidazole was obtained as an amber coloured solid (94 parts).

Infra red spectrum (nujol) 3350, 1730 and  $1660\text{ cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 2.7 (s, 4H), 3.75 (s, 3H), 8.65 (d, 1H), 9.55 (d, 1H).

- (b) A mixture of dimethylhydrazine (11.8 parts) propylene oxide (12.5 parts), sodium methoxide (8 parts) and t-butyl alcohol (120 parts) was treated with the methyl ester obtained in (a) above (46 parts) and the mixture stirred overnight at a temperature of  $60^{\circ}\text{C}$ . The solvent was removed, methanol was added and the solution filtered. Benzene was added to the filtrate and the mixture evaporated to dryness. The residual solid was collected and washed several times with ether to give the title

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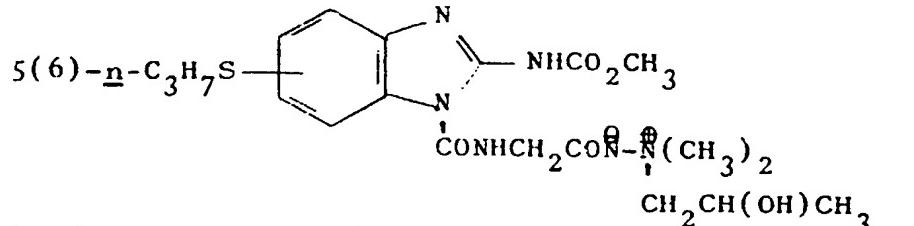
- 33 -

aminimide as a hygroscopic, water soluble, tan coloured solid (71 parts). Infra red spectrum (nujol)  $1650\text{ cm}^{-1}$  (amide carbonyl) and  $1570\text{ cm}^{-1}$  (aminimide carbonyl).

Example 7

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Preparation of



Aminimide derived from methyl 5(6)-n-propylthiobenzimidazole-1-methoxycarbonylmethylamino-carbonyl-2-carbamate (10).

(a) A slurry of methyl 5(6)-n-propylthiobenzimidazole-2-carbamate (1.5 g) in methylene chloride (15 ml) was treated at room temperature with methyl isocyanatoacetate (0.82 g) and the mixture was allowed to stir for 3 hr. The solvent was removed by distillation, diethyl ether (30 ml) was added and the mixture was stirred until the product was crystalline. The pale pink solid was collected and was washed with cold ether to give methyl 5(6)-n-propylthiobenzimidazole-1-methoxycarbonylmethylaminocarbonyl-2-carbamate in 77% yield (1.65g), Infra red spectrum (nujol) 3230, 1730, 1715, 1660, 1640 and  $1620\text{ cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 1.0 (s, 3H), 2.85 (s, 2H) 1.6 (m, 2H), 4.75 (s, 3H), 4.85 (s, 3H), 4.2 (d, 2H).

(b) A mixture of dimethylhydrazine (7.1 parts), propylene oxide (7.5 parts) and isopropyl alcohol (200 parts) was heated at a temperature of 70°C in an oil bath for 1.0 hr. The ester obtained in (a) above (38 parts) was added and the mixture heated at a temperature of 80°C during 72 hr. The solvent was removed by distillation to afford the title aminimide as a viscous water soluble, amber coloured oil.

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Infra red spectrum (film) 3200, 1705 and 1650-1600  $\text{cm}^{-1}$ .

Example 8

(a) Methyl 5(6)-phenylthiobenzimidazole-1-methoxy carbonyl-methylaminocarbonyl-2-carbamate, methyl 5(6)-phenyl-sulfinylbenzimidazole-1-methoxycarbonylmethylamino-carbonyl-2-carbamate and methyl 5(6)-(p-hydroxyphenylthio)-benzimidazole-1-methoxycarbonylmethylaminocarbonyl-2-carbamate were prepared from the corresponding benzimidazoles following an analogous procedure to that described in Example 7 for the preparation of methyl 5(6)-n-propylthiobenzimidazole-1-methoxycarbonylmethylamino-carbonyl-2-carbamate from methyl 5(6)-n-propylthio-benzimidazole-2-carbamate.

Methyl 5(6)-phenylthiobenzimidazole-1-methoxycarbonyl-methylaminocarbonyl-2-carbamate:

White crystalline powder

Infra red spectrum (nujol) 3250, 1740, 1720, 1665 and

1620  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 3.75 (s, 6H), 4.2 (d, 2H),  
7.2-7.4 (7 H), 8.1-8.3 (1H)

Methyl 5(6)-phenylsulfinylbenzimidazole-1-methoxycarbonyl-  
methylaminocarbonyl-2-carbamate:

White crystalline powder

Infra red spectrum (nujol) 3200, 1750, 1710, 1665, 1605  $\text{cm}^{-1}$ .

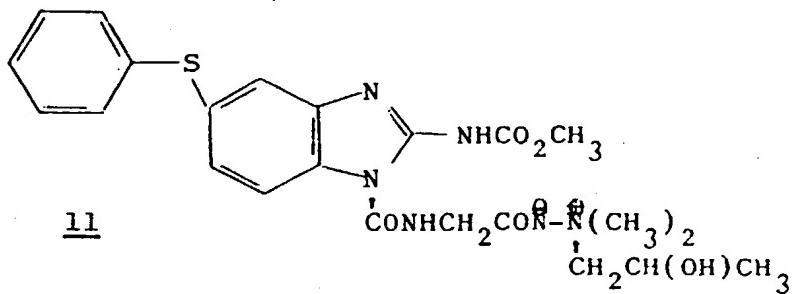
Methyl 5(6)-(p-hydroxyphenylthio)benzimidazole-1-  
methoxycarbonylmethylaminocarbonyl-2-carbamate:

White crystalline powder

Infra red spectrum (nujol) 3350, 3250, 1750, 1725-1710,  
1640, 1615  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm) 3.8 (s, 6H), 4.2. (d, 2H),  
6.7-7.6 (m, 5H), 7.8-8.4 (m, 2H).

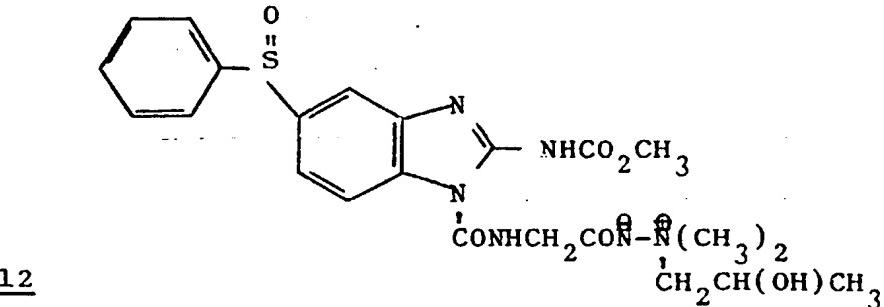
- (b) The aminimides 11, 12 and 13 were prepared from the 1-substituted benzimidazole carbamates described in (a) above following an analogous procedure to that described in Example 7 for the preparation of the aminimide 10 from methyl 5(6)-n-propylthiobenzimidazole-1-methoxycarbonylmethylaminocarbonyl-2-carbamate.



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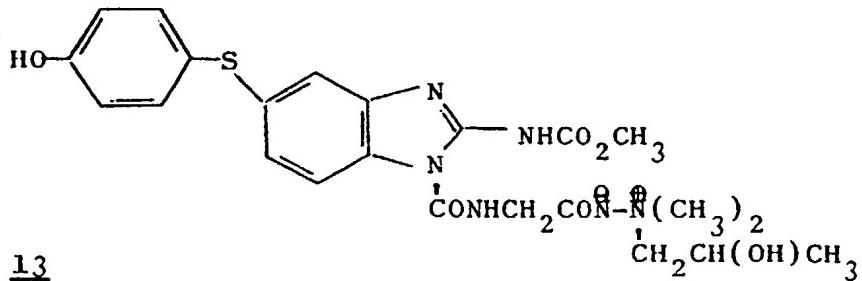
Viscous, water soluble, oil.

Infra red spectrum (film) 3300, 1710, 1650-1600  $\text{cm}^{-1}$ .



Viscous, water soluble, oil

5 Infra red spectrum (film) 3300, 1710 and 1650-1600  $\text{cm}^{-1}$ .

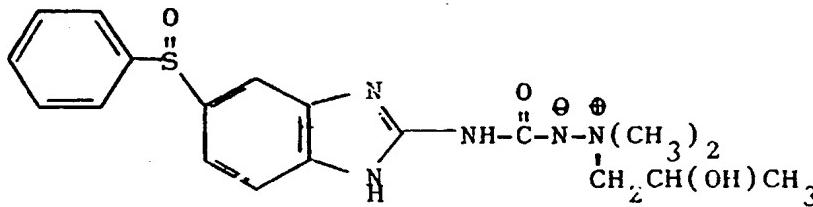


Viscous, water soluble, oil

Infra red spectrum (film) 3300, 1710, 1650-1600  $\text{cm}^{-1}$ .

Example 9

10 Preparation of



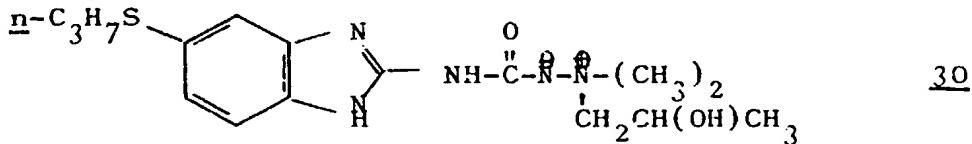
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A mixture of unsymmetrical dimethylhydrazine (4.0 ml), propylene oxide (4.0 ml) and isopropanol (40 ml) was heated at a temperature of 80°C for a period of one hour. Methyl 5(6)-phenylsulfinylbenzimidazole-2-carbamate (4.07 g) was added directly to the stirred mixture and heating at a temperature of 65°C was continued for a period of 48 hours. The mixture was filtered, the solvent was removed by distillation under reduced pressure and the residue was heated under reduced pressure to constant weight (40°C, 0.01 mm Hg, 3-4 hr). The product was a water soluble, pink glossy solid (9.46 g) which by thin layer chromatography showed no starting material.

Infrared spectrum (nujol) 3200-3400, 1580-1660  $\text{cm}^{-1}$ .

Example 10

### **Preparation of**



A mixture of unsymmetrical dimethylhydrazine (4.4 ml), propylene oxide (4.4 ml) and isopropanol (44 ml) was heated at a temperature of 80°C for a period of one hour. Methyl 5(6)-n-propylthiobenzimidazole-2-carbamate (3.76 g) was added directly to the stirred mixture and heating was continued at a temperature of 65°C for a period of 48 hours. The mixture was filtered, the solvent was removed by distillation under

reduced pressure and the residue was heated under reduced pressure to constant weight ( $40^{\circ}\text{C}$ , 0.01 mm Hg, 3-4 hr).

The product was a water-soluble, dark red, viscous liquid (9.27 g) which by thin layer chromatography and proton magnetic resonance analysis showed no starting material.

Infra red spectrum (film) 3300, 1580--1660  $\text{cm}^{-1}$ .

Partial pmr spectrum ( $\delta$  ppm in trifluoroacetic acid) 7.4-8.4 (m, Ar-H), (no resonance at 3.8 for  $\text{NHCO}_2\text{CH}_3$ ).

Example 11

Sterile aqueous solutions (5% w/v active ingredient) were prepared by dissolving each of the following compounds of the invention in distilled water and sterilising the resultant solution by ultrafiltration.

TABLE I

Compound No	Structure
<u>10</u>	<p style="text-align: center;"> <math>\text{5(6)-n-C}_3\text{H}_7\text{S}-</math>    <math>\text{CONHCH}_2\text{CON}-\text{N}(\text{CH}_3)_2</math>  <math>\text{CH}_2\text{CH(OH)CH}_3</math> </p>
<u>12</u>	<p style="text-align: center;"> <math>\text{5(6)-C}_6\text{H}_5\text{S}-</math>    <math>\text{CONHCH}_2\text{CON}-\text{N}(\text{CH}_3)_2</math>  <math>\text{CH}_2\text{CH(OH)CH}_3</math> </p>
<u>20</u>	<p style="text-align: center;"> <math>\text{NHCH}_2\text{CON}-\text{N}(\text{CH}_3)_2</math>  <math>\text{CO}</math>  <math>\text{NH}</math>    <math>\text{Na}^+</math>  <math>\text{CH}_2\text{CH(OH)CH}_3</math> </p>
<u>23</u>	<p style="text-align: center;"> <math>\text{CH}_2\text{CH}_2\text{CON}-\text{N}(\text{CH}_3)_2</math>  <math>\text{CO}</math>  <math>\text{NH}</math>    <math>\text{Na}^+</math>  <math>\text{CH}_2\text{CH(OH)CH}_3</math> </p>
<u>29</u>	<p style="text-align: center;"> <math>\text{C}_6\text{H}_5\text{S}-</math>    <math>\text{NH-C(=O)-R-N}(\text{CH}_3)_2</math>  <math>\text{CH}_2\text{CH(OH)CH}_3</math> </p>

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Example 12

Each of the sterile solutions described in Example 11 were used to dose sheep suffering from a natural mixed infection of helminths.

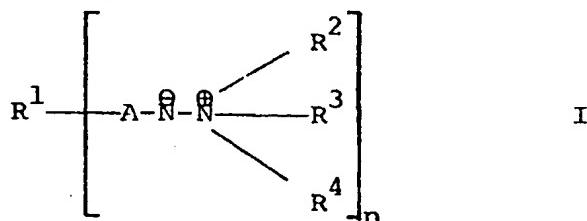
5 The sheep were dosed by subcutaneous injection and the dose rate and results are shown in Table II.

TABLE II

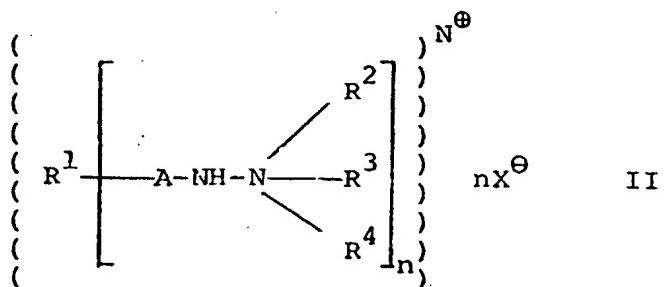
Compound No	Dose Rate mg/kg	Faecal Egg Count (Haemonchus) Eggs/g faeces (day)
<u>10</u>	12.0	900(0) 100(2) 0(7)
<u>12</u>	18.0	3000(0) 0(2) 0(7) (No worms on post-mortem)
<u>20</u>	50.0	800(0) 0(2) 100(7)
<u>23</u>	100.0	6800(0) 3400(2) 0(7)
<u>29</u>	13.25	4600(0) 3100(2) 0(7) (No worms on post-mortem)

The claims defining the invention are as follows:-

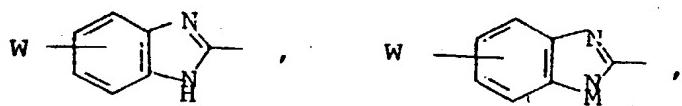
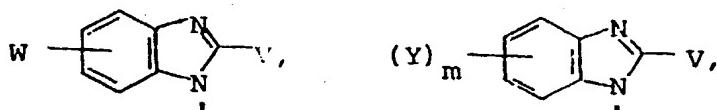
1. A water soluble aminimide of general formula I:

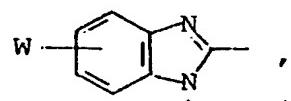
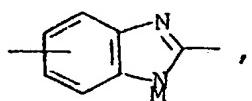
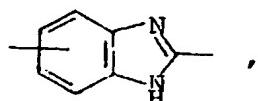
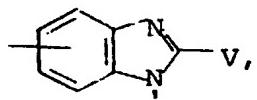
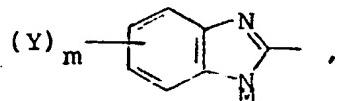
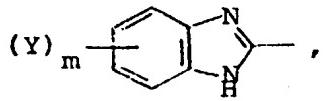


and the acid addition salt therefore of general formula II:

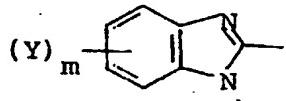


wherein R<sup>1</sup> is a benzimidazole chosen from





and

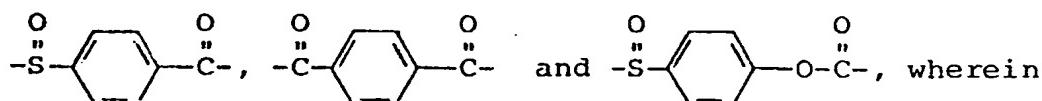
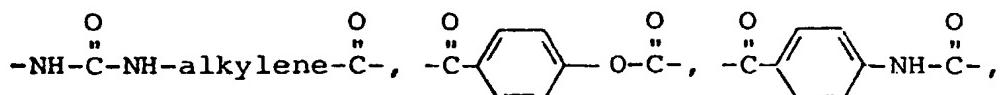
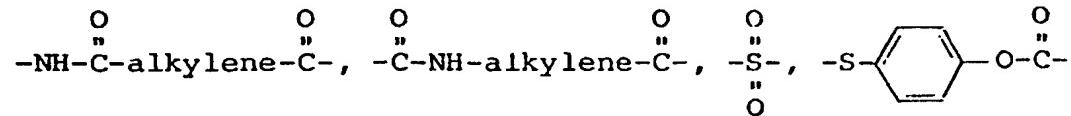
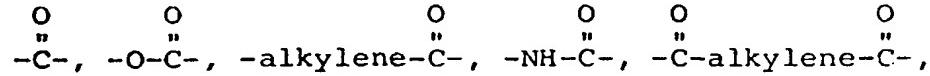


wherein W is hydrogen,

nitro, trifluoromethyl,  $C_1$  to  $C_8$  alkyl,  $C_1$  to  $C_8$  alkoxy,  $C_1$  to  $C_8$  alkylthio, amino, hydroxylamino,  $NHCO_2CH(CH_3)_2$ , phenylthio, 4-aminophenylthio, 4-hydroxyphenylthio, phenylsulfinyl, 4-aminophenylsulfinyl, 4-hydroxyphenylsulfinyl, phenylsulfonyl, 4-aminophenylsulfonyl, 4-hydroxyphenylsulfonyl, benzoyl;

Y is halogen and m is an integer from 1 to 4; V is chosen from trifluoromethyl, 4-thiazolyl, 2-furyl and  $NHCO_2T$

wherein T is C<sub>1</sub> to C<sub>6</sub> alkyl; and M is the cation of an organic or inorganic base; A is chosen from

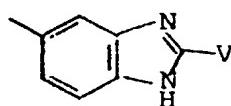


alkylene is a C<sub>1</sub> to C<sub>6</sub> alkylene group;

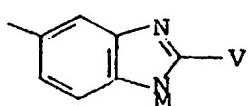
R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently chosen from C<sub>1</sub> to C<sub>6</sub> alkyl, 2-hydroxy substituted C<sub>2</sub> to C<sub>6</sub> alkyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl, C<sub>6</sub> cycloalkyl, allyl, benzyl and phenyl; X<sup>θ</sup> is a pharmaceutically acceptable anion; n is an integer from 1 to 3; and when n is 2 or 3 the groups -A-N<sup>θ</sup>-NR<sup>2</sup>R<sup>3</sup>R<sup>4</sup> may be the same or different.

2. An aminimide according to claim 1 wherein:

R<sup>1</sup> is chosen from

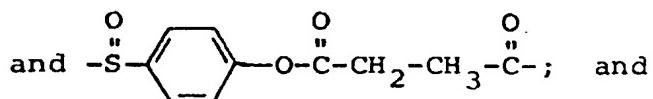
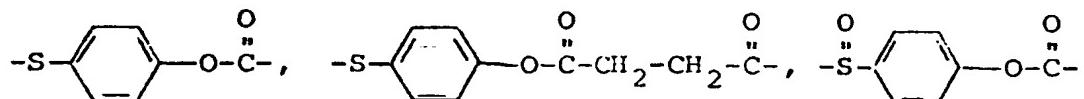
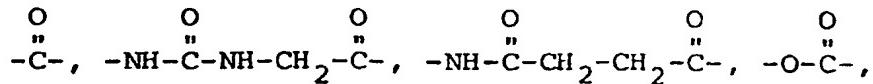


and



wherein V is chosen from trifluoromethyl, 4-thiazolyl, and the group  $\text{NHCO}_2\text{T}$  wherein T is  $\text{C}_1$  to  $\text{C}_6$  alkyl, and M is an alkali metal or alkaline earth metal cation;

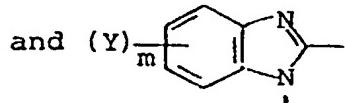
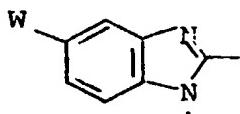
A is chosen from



$\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are independently chosen from methyl, ethyl 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl and allyl.

3. An aminimide according to claim 1 wherein:

$\text{R}^1$  is chosen from



wherein V is chosen from trifluoromethyl, 4-thiazolyl and the group  $\text{NHCO}_2\text{T}$  wherein T is  $\text{C}_1$  to  $\text{C}_6$  alkyl, W is chosen from hydrogen, nitro,  $\text{C}_1$  to  $\text{C}_8$  alkylthio, or a phenylthio, phenylsulfinyl or phenylsulfonyl group in which each group is optionally substituted on the phenyl ring with an amino

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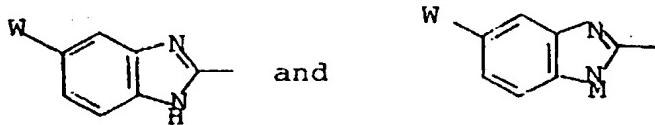
or hydroxy substituent, Y is halogen and m is an integer from 1 to 4;

A is chosen from  $-\text{CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,  $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-NH-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,  $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$  and  
 $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}\text{-CH}_2\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ; and

$\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are independently chosen from methyl, ethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl and allyl.

4. An aminimide according to claim 1 wherein:

$\text{R}^1$  is chosen from



wherein W is chosen from hydroger., nitro,  $\text{C}_1$  to  $\text{C}_8$  alkylthio, or a phenylthio, phenylsulfinyl or phenylsulfonyl group in which each group is optionally substituted on the phenyl ring with an amino or hydroxy substituent, and M is an alkali metal or alkaline earth metal cation;

A is  $-\text{NH}\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ; and

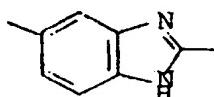
$\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  are chosen from methyl, ethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-chloro-2-



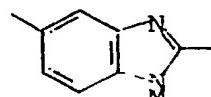
hydroxypropyl and allyl.

5. An aminimide according to claim 1 wherein:

R<sup>1</sup> is chosen from



and



wherein M is an alkali metal or alkaline earth metal cation;

A is chosen from -C(=O)-, -CH<sub>2</sub>-C(=O)-, -C(=O)-NH-CH<sub>2</sub>-C(=O)-,

-NH-C(=O)-NH-CH<sub>2</sub>-C(=O)-, -NH-C(=O)-CH<sub>2</sub>-CH<sub>2</sub>-C(=O)-, -O-C(=O)-, -S--O-C(=O)-,

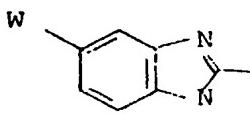
-S--O-C(=O)-CH<sub>2</sub>-CH<sub>2</sub>-C(=O)-, -S--O-C(=O)-,

-S--O-C(=O)-CH<sub>2</sub>-CH<sub>2</sub>-C(=O)- and -NH-C(=O)-; and

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently chosen from methyl, ethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl and allyl.

6. An aminimide according to claim 1 wherein:

R<sup>1</sup> is chosen from



and



wherein W is chosen from hydrogen, nitro, C<sub>1</sub> to C<sub>8</sub> alkyl-thio or a phenylthio, phenylsulfinyl or a phenylsulfonyl group in which each group is optionally substituted on the phenyl ring with an amino or a hydroxy substituent, Y is halogen and m is an integer from 1 to 4;

A is chosen from  $-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,  $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-\text{NH}-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,  $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-\text{CH}_2-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,

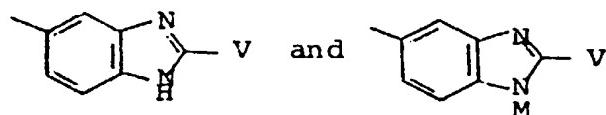
$-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-\text{CH}_2-\text{C}-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$  and  $-\text{NH}-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ; and

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently chosen from methyl, ethyl, 2-hydroxyethyl, 2-hydroxypropyl, 2,3-dihydroxypropyl, 3-chloro-2-hydroxypropyl and allyl.

7. An aminimide according to claim 1 or claim 2

wherein:

R<sup>1</sup> is chosen from



wherein V is trifluoromethyl or 4-thiazolyl and M is an alkali metal cation; when V is 4-thiazolyl A is chosen

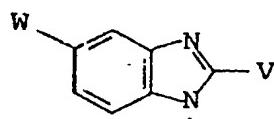
from  $-\overset{\text{O}}{\underset{\text{''}}{\text{NH}}}-\text{C}-\overset{\text{O}}{\underset{\text{''}}{\text{NH}}}-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$  and  $-\overset{\text{O}}{\underset{\text{''}}{\text{NH}}}-\text{C}-\overset{\text{O}}{\underset{\text{''}}{\text{CH}_2}}-\text{CH}_2-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ,

and when V is CF<sub>3</sub> A is  $-\overset{\text{O}}{\underset{\text{''}}{\text{C}}}-$ ; and R<sup>2</sup> and R<sup>3</sup> are each methyl and R<sup>4</sup> is 2-hydroxypropyl.

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8. An aminimide according to claim 1 or claim 3  
wherein:

R<sup>1</sup> is



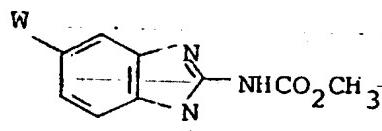
wherein W is H and V is trifluoromethyl or 4-thiazolyl or  
W is nitro and V is trifluoromethyl;

A is  $-\text{CH}_2-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-$ ; and

R<sup>2</sup> and R<sup>3</sup> are each methyl and R<sup>4</sup> is 2-hydroxypropyl.

9. An aminimide according to claim 1 or claim 3  
wherein:

R<sup>1</sup> is



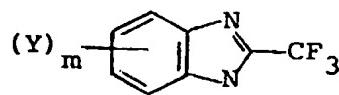
wherein W is n-propylthio, phenylthio, phenylsulfinyl or  
4-hydroxyphenylthio;

A is  $-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{NH}-\text{CH}_2-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-$ ; and

R<sup>2</sup> and R<sup>3</sup> are each methyl and R<sup>4</sup> is 2-hydroxypropyl.

10. An aminimide according to claim 1 or claim 5  
wherein:

R<sup>1</sup> is



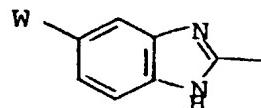
wherein Y is chloro or bromo and m is 4;

A is -CH<sub>2</sub>-C(=O)-; and

R<sup>2</sup> and R<sup>3</sup> are each methyl and R<sup>4</sup> is 2-hydroxypropyl.

11. An aminimide according to claim 1 or claim 4  
wherein:

R<sup>1</sup> is



wherein W is n-propylthio or phenylsulfinyl;

A is -NH-C(=O)-; and

R<sup>2</sup> and R<sup>3</sup> are each methyl and R<sup>4</sup> is 2-hydroxypropyl.

12. A process for the preparation of a water-soluble aminimide of formula I or formula II as defined according to any one of claims 1 to 11 inclusive which process comprises reacting a water insoluble organic compound comprising a benzimidazole and an acid ester group



with hydrazine, a monosubstituted hydrazine or an unsymmetrically disubstituted hydrazine and an alkylene oxide to form said water soluble aminimide.

13. A process for the preparation of a water-soluble aminimide of formula I or formula II as defined according to any one of claims 1 to 11 inclusive wherein hydrazine, a mono-substituted hydrazine or an unsymmetrically di-substituted hydrazine is reacted with an alkylene oxide to form an aminimine and said aminimine is reacted with a water insoluble compound comprising a benzimidazole and an acid ester group to form said water soluble aminimide.

14. A process for the preparation of a water-soluble aminimide of formula I or formula II as defined according to any one of claims 1 to 11 inclusive wherein a water insoluble organic compound comprising a benzimidazole and an acid ester or acid halide group is reacted with hydrazine, a mono-substituted hydrazine or an unsymmetrically di-substituted hydrazine to form an acid hydrazide derivative and said acid hydrazide derivative is reacted with an alkylating agent to form said water soluble aminimide.

15. A process for the preparation of a water-soluble aminimide of formula I or formula II as defined according to any one of claims 1 to 11 inclusive wherein a water insoluble organic comprising a benzimidazole ring and an acid ester or acid halide group is reacted with a 1,1,1-tri-substituted hydrazinium salt in the presence of a base to form said



water soluble aminimide.

16. A method of treating warm-blooded animals to eradicate helminths which method comprises administering to said warm-blooded animal a therapeutic dose of a composition comprising as active ingredient an aminimide of general formula I or acid addition salt thereof of general formula II as defined according to any one of claims 1 to 13 inclusive and an inert carrier therefor.

17. A method according to claim 16 wherein the helminths are nematodes of the Haemonchus spp.

18. A method according to claim 16 or claim 17 wherein the composition is administered in a single dose at a dosage level in the range from 1 to 100 mg of active ingredient per kilogram of animal body weight.

19. A method according to claims 16 to 18 inclusive wherein the dose is administered parenterally.

20. A composition comprising as active ingredient an aminimide of general formula I or acid addition salt thereof of general formula II as defined according to any one of claims 1 to 11 inclusive and an inert carrier therefor.

21. A sterile injectable aqueous composition according to claim 20 wherein the active ingredient comprises from 5 to 80% by weight of the composition.

22. A compound according to any one of claims 1 to 11 inclusive substantially as described with reference to any one of Examples 1 to 10 inclusive.

23. A process according to any one of claims 12 to 15 inclusive substantially as described with reference to any one of Example 1 to 10 inclusive.

24. A process according to any one of claims 16 to 19 inclusive substantially as described with reference to Example 12.

25. A composition according to claim 20 or claim 21 substantially as described with reference to Example 11.

DATED this

1<sup>st</sup> day of October 19<sup>78</sup>

ICI AUSTRALIA LIMITED